# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| OOS-001-PCT | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/EP 03/07270 | 07.07.2003 | 08.07.2002 |
| International Patent Classification (IPC) or both national classification and IPC | | |
| A61K35/78 | | |
| Applicant | | |
| D'OOSTERLYNCK, André | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

EPO - DG 1

03. 12. 2004

(52)

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 02.02.2004 | 21.10.2004 |
| Name and mailing address of the international preliminary examining authority: | Authorized Officer |
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Thalmair, M<br>Telephone No. +49 89 2399-2177 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07270

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-45 as originally filed

**Claims, Numbers**

1-25 received on 05.07.2004 with letter of 05.07.2004

**Drawings, Sheets**

1/11-11/11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 24-25 (industrial applicability)

because:

☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-25 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-25 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-23 |
| | No: | Claims | 24-25 see Separate Sheet |

2. Citations and explanations

see separate sheet

**Section III**

Claims 24-25 relate to a subject-matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34 (4) a) (i) PCT).

**Section V**

The subject-matter of claims 1-14, 18 is considered as being novel and inventive, since the use of a simmondsin, stereoisomeric forms, racemic mixtures, metabolites, esters or salts thereof or mixtures thereof or the use of a compound having the general formula (I) for the manufacture of a medicament for inhibiting angiogenesis or angiogenesis-related diseases has neither been disclosed nor suggested by the prior art as cited in the International Search Report.

Furthermore, also the subject-matter of claims 15-17, 20-23 is regarded as being novel for the following reasons.

**D 2** (Hanan M. Sobhy and Elham A. Mohamed, 1996) refers to a medicinal activity of crude jojoba oil, namely anti-bacterial, anti-parasitic, antipyretic and anti-inflammatory effects thereof, whereas the present application refers to the use of isolated specific simmondsin compounds or a polar extract of jojoba flour as a medicament. On page 4, line 22-25 of the present application it is explained that the oil fraction is removed, and the remaining dry matter is extracted to result in a polar extract, c.f. claim 17. The use of jojoba oil as a medicament, however, is not claimed in the present application.

**D 1** (WO 94/25035) describes the use of simmondsin, derivatives and/or analogues thereof as medicament. D 1 relates to the use of all possible simmondsin derivates for this activity, but D 1 only explicitly refers to simmondsin (i.e. 4,5-dimethylsimmondsin), simmondsin-2'-ferulate (i.e. 4,5-dimethylsimmondsi-2'-ferulate), a-glucons of simmondsins and de-oiled jojoba flour. Applicant has acknowledged the use of 4,5-dimethylsimmondsin(-2'-ferulate) as a medicament by introducing a disclaimer in the wording of claims 15 and 20, for which there is a basis in the description, see e.g. page 27, line 11-15 thereof.

But the general disclosure of D 1 does not anticipate the novelty of the specific disclosure of the present application. D 1 discloses the use of simmondsins in general, but not the specific use of certain specific compounds.

With regard to inventiveness, medicinal activities of certain simmondsin derivatives or jojoba extracts may not be extrapolated to all simmondsin derivatives or jojoba extracts in general, especially in view of Flo et al. (1998), provided by Applicant in his letter of May 7,

2004, who demonstrated that only 4,5-dimethylsimmondsin and its ferulate show medicinal (appetite-inhibiting) effects, and that appetite-inhibiting effects could not be demonstrated for the specific compounds 4-desmethylsimmondsin and 4,5-didesmethylsimmondsin. There is no hint in D 1 or D 2 that other specific simmondsin compounds or extracts of jojoba could be applied as a medicament, especially in view of Flo et al. which teaches away there from that other specific simmondsin compounds as those disclosed in D 1 or D 2 may be used as a medicament.

In addition, the angiogenesis-inhibiting activity of the specific compounds as claimed was unexpected and not derivable from the available prior art.

**Claims without indication of amendments**

1. Use of a simmondsin, stereoisomeric forms, racemic mixtures, metabolites, esters or salts thereof, or mixtures thereof for the manufacture of a medicament for inhibiting angiogenesis.

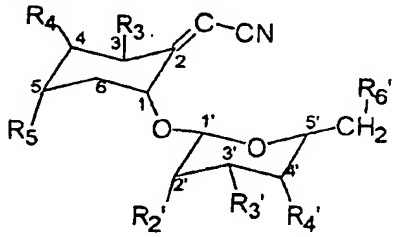
2. Use according to claim 1, whereby said simmondsin naturally occurs in jojoba and is comprised within jojoba flour or a jojoba extract.

3. Use according to claim 1 or 2, whereby said simmondsin is selected from the group comprising 4-desmethylsimmondsin, 5-desmethylsimmondsin, 4,5-didesmethylsimmondsin, 4,5-dimethylsimmondsin, stereoisomeric forms, racemic mixtures, metabolites, esters or salts thereof, or any mixtures thereof.

4. Use according to any of claims 1-3 wherein said esters are ferulates.

5. Use according to any of claims 1-4, whereby said simmondsin is selected from the group comprising 4-desmethylsimmondsin, 5-desmethylsimmondsin, 4,5-didesmethylsimmondsin, 4-desmethylsimmondsin-2'-ferulate, 5-desmethylsimmondsin-2'-ferulate, 4,5-didesmethylsimmondsin-2'-ferulate, 4,5-dimethylsimmondsin-2'-ferulate, and any mixtures thereof.

6. Use of a compound having general formula (I)




Formula (I)

and stereoisomeric forms, racemic mixtures, metabolites, esters, salts, or mixtures thereof, for the manufacture of a medicament for inhibiting angiogenesis,

wherein $R_4$ and $R_5$ are independently selected from the group comprising oxo, hydrogen, hydroxyl, alkyl, alkenyl, alkynyl, alkyloxy, alkyloxyalkyl, alkylthioalkyl, alkyloxycarbonyl, alkylthiocarbonyl, alkanoyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylthiocarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkoxythiocarbonyl, cycloalkylthioalkyl,

alkylcarbonyloxyalkyl, arylcarbonyloxyalkyl, cycloalkylcarbonyloxyalkyl, silyloxyalkyl, aryl, aralkyl, arylalkenyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalkyl, arylthioalkyl, haloalkyl, hydroxyalkyl, aralkanoyl, aroyl, aryloxycarbonylalkyl, aryloxyalkanoyl, carboxyl, formyl, alkenylcarbonyl, alkynylcarbonyl, cyano, aminocarbonyl, aminoalkanoyl, aminoalkyl, $CR^6=NR^7$ or $CR^6=N(OR^7)$, with $R^6$ and $R^7$ being independently selected from the group comprising hydrogen, hydroxyl, alkyl, aryl, alkenyl, alkynyl, aminoalkyl, aminoaryl, alkylcarbonylamino, arylcarbonylamino, alkylthiocarbonylamino and arylthiocarbonylamino; and

wherein $R_3$, $R_2'$, $R_3'$ $R_4'$, and $R_6'$ are independently selected from the group comprising hydroxyl or an ester.

7. Use of a compound having general formula (I) according to claim 6, wherein $R_4$ and $R_5$ are independently selected from the group comprising oxo, hydrogen, hydroxyl, alkyl, alkenyl, alkynyl, alkyloxy, alkyloxyalkyl, alkylthioalkyl, alkyloxycarbonyl, alkylthiocarbonyl, alkanoyl, lkylcarbonyloxyalkyl, arylcarbonyloxyalkyl, silyloxyalkyl, haloalkyl, hydroxyalkyl, carboxyl, formyl, alkenylcarbonyl, alkynylcarbonyl, cyano, aminocarbonyl, aminoalkanoyl, aminoalkyl, and wherein $R_3$, $R_2'$, $R_3'$ $R_4'$, and $R_6'$ are independently selected from the group comprising hydroxyl or an ester.

8. Use of a compound having general formula (I) according to claim 6 or 7, wherein $R_4$ and $R_5$ are independently selected from the group comprising hydroxyl, alkyl, alkyloxy, and wherein $R_3$, $R_2'$, $R_3'$ $R_4'$, and $R_6'$ are independently selected from the group comprising hydroxyl or an ester.

9. Use of a compound having general formula (I) according to any of claims 6-8, wherein $R_4$ and $R_5$ are independently selected from the group comprising hydroxyl, and $-OCH_3$, and wherein $R_3$, $R_2'$, $R_3'$ $R_4'$, and $R_6'$ are independently selected from the group comprising hydroxyl or an ester.

10. Use of a compound having general formula (I) according to any of claims 6-9, wherein said ester is a ferulate.

11. Use of a simmondsin, stereoisomeric forms, racemic mixtures, metabolites, esters or salts thereof, or mixtures thereof for the manufacture of a medicament for treating angiogenesis-related diseases.

12. Use according to claim 11, whereby said simmondsin naturally occurs in jojoba and is comprised within jojoba flour or a jojoba extract.

13. Use according to claims 11 or 12, whereby said simmondsin is selected from the group comprising 4-desmethylsimmondsin, 5-desmethylsimmondsin, 4,5-didesmethylsimmondsin, 4-desmethylsimmondsin-2'-ferulate, 5-desmethylsimmondsin-2'-ferulate, 4,5-didesmethylsimmondsin-2'-ferulate, 4,5-dimethylsimmondsin-2'-ferulate, and any mixtures thereof.

14. Use of a compound having general formula (I) as defined in claim 6, for the manufacture of a medicament for treating angiogenesis-related diseases.

15. A simmondsin having general formula (I), as defined in claim 6, with the exception of 4,5-dimethylsimmondsin and 4,5-dimethylsimmondsin-2'-ferulate for use as a medicament.

16. Use of 4-desmethylsimmondsin, 5-desmethylsimmondsin, 4,5 didesmethylsimmondsin, 4-desmethylsimmondsin-2'-ferulate, 5-desmethylsimmondsin-2'-ferulate, and 4,5-didesmethylsimmondsin-2'-ferulate, as a medicament.

17. Polar extract from jojoba flour for use as a medicament.

18. Use of jojoba flour or an extract from jojoba flour for the manufacture of a medicament for inhibiting angiogenesis.

19. Use of jojoba flour or an extract from jojoba flour for the manufacture of a medicament for treating angiogenesis-related diseases.

20. A pharmaceutical composition for inhibiting angiogenesis or for treating angiogenesis-related diseases comprising a therapeutically effective amount of a compound as defined in claim 6 with the exception of 4,5-dimethylsimmondsin and 4,5-dimethylsimmondsin-2'-ferulate and a pharmaceutically acceptable excipient.

21. Pharmaceutical composition according to claim 20, wherein said pharmaceutical composition is formulated to be applied orally.

22. Pharmaceutical composition according to claim 20, wherein said pharmaceutical composition is formulated to be applied parentally.

23. Pharmaceutical composition according to claim 20, wherein said pharmaceutical composition

is formulated to be applied topically.

24. Method of inhibiting angiogenesis in humans and animals comprising administering to the human or animal in need thereof a therapeutically effective amount of a compound as defined in claim 6.

25. Method of treating an angiogenesis-related disease in humans and animals comprising administering to the human or animal in need thereof a therapeutically effective amount of a compound as defined in claim 6.